Improving Outcomes in *HER2*+ Breast Cancer: Analysis and Application of Evolving Data and Best Practices

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JOSH EPWORTH Good evening and welcome to this certified dinner symposium. My name is Josh Epworth, and our focus tonight is Improving Outcomes in *HER2*+ Breast Cancer: Analysis and Application of Evolving Data and Best Practices. Please allow me to introduce your speakers for this evening: Dr. Jame Abraham and Ms. Kelley Mayden. Dr. Abraham is the Director of Breast Oncology Program at Taussig Cancer Institute and Co-Director of the Cleveland Clinic Comprehensive Breast Cancer Program. Dr. Abraham is also a professor of medicine at the Cleveland Clinic Learner College of Medicine. He serves in the NCCN Breast Cancer Committee, is Vice Chair at the NRG Oncology Research Strategy Committee, and is Vice Chair of the Research Review Committee for the National Surgical Adjuvant Breast and Bowel Project. Ms. Mayden is an advanced practice provider at Ballad Health Cancer Care. She has 33 years of nursing experience, 10 of which as an oncology nurse, and 19 as an oncology and hematology advanced practice provider. She maintains an active practice seeing a variety of patient types and runs the Bone Marrow Center for her Clinic. Her interests include breast cancer, multiple myeloma, symptom management, benign hematologic, and cancer cause containment. Please join me in welcoming both of them to the stage.

MS. MAYDEN Good evening everyone and welcome. Wow. This is amazing to look out and see so many people here. It kind of reminds me of a quote from Oliver Wendell Holmes Jr., who once said “A man’s mind expanded by new ideas can never return to its original dimensions.” I think after all the power-packed learning in these last few days, it’s pretty safe to say we have pretty much expanded our dimensions. I'm glad to see you're here tonight with an appetite for more learning. I'm confident when I say that tonight’s presentation will quench your thirst for more knowledge and add to your evidence base. I say that based on the fact that I have seen what goes on behind the scenes from *JADPRO*, APSHO, Harborside Press, to bring this to you and put this together. And, as if that weren’t enough, we are privileged to have with us tonight Dr. Jame Abraham, and it's my honor to share the stage with him. I really simply like to rather refer to him as the human encyclopedia of breast cancer. With that said, we will get started.

These are our disclosures. We will have some off-label conversation this evening. If you have any questions about that, you can always refer to any package inserts. Mainly, what we want to do tonight is focus on *HER2*/neu-positive breast cancer. Looking at this population, we want to examine what the current evidence is, look at the emerging evidence, and see how that can help us improve our treatment plans for our patients. We will look specifically at CNS metastases and looking at plans for that, because we know women with *HER2*/neu-positive breast cancer are at risk for recurrence. About one in four, and about 50% of those recurrences will be a brain metastasis, so it is a very

important topic for these ladies. The last thing we will do is just briefly talk a little bit about managing some adverse events associated with our *HER2*/neu-positive therapies.

We are going to start talking about the current standards of care. It's always a good place to start, but I think before we talk about the current standards of care in *HER2*/neu-positive breast cancer, there is some room for some reflection on the breast cancer space as a whole. We know that breast cancer has a deep and rich history, and that the theater is characterized by multiple canopies, which have all coalesced to give us a decrease in breast cancer mortality since at least the year 2000. When we think about the number of women who will be diagnosed this year, greater than 268,000, and the number of deaths greater than 40,000, what we know from that is we have done well. Women are living longer, and we have done better, but we still can't say that this is a completely curable disease. Knowing that and knowing that *HER2*/neu-positive breast cancer tends to occur in younger women, and it is an aggressive phenotype, it tends to be more poorly undifferentiated when it does present. As advanced practice providers, it just calls us to come to the table knowing all of our options, understanding the data, and being able to put together a care plan for our patients from the very beginning of their therapy. A long-term plan for these patients. That's what we are going to talk about tonight: how best to do that.

Again, *HER2*/neu-positive breast cancer – you can see the percentages here and the prevalence does occur in our younger women. That aggression that

I spoke about, when you think about it, people that know me and have heard me talk about *HER2*/neu-positive aggression know that I always refer to a quote by Jimmy Carter. And I also say, I am not playing politics, it's not my thing, but he did say “Aggression unopposed becomes a contagious disease.” Aggression unopposed, *HER2*/neu-positive breast cancer, will become a contagious disease will be recurrent malignant *HER2*/neu-positive breast cancer, which is uncurable and associated with shortened progression-free survival and overall survival.

Current standards of care: What do we have and where are we? When we look across settings in the early-stage adjuvant and neoadjuvant setting, we know we commonly used trastuzumab plus chemotherapy, or trastuzumab, plus pertuzumab, plus chemotherapy in the neoadjuvant setting, that driven by TRYPHAENA and NeoSphere, which Dr. Abraham will cover for us. Also, in the adjuvant setting, APHINITY more recently, people are using the combination. Looking at people who cannot get a pathological complete response from the neoadjuvant setting, now moving those patients to T-DM1 from the KATHERINE trial. Now we also have data and approval for a small molecule tyrosine kinase inhibitor, neratinib, which is for use in the extended adjuvant setting. It's the only drug approved for that, and the first of its kind, so I think this is a real victory for women, because now we have that extended adjuvant setting. It is the period that we used to watch and worry, watch and wait, and now we can be aggressive and mobilized for treatment.

Metastatic breast cancer – not everybody will get cured. We have had these traditional standards of care: first-line taxane, trastuzumab, and

pertuzumab. Second-line T-DM1, and third-line lapatinib plus capecitabine. I think you will hear from the data tonight this has been supported, but it may be changing in the near future. With that, I will welcome our esteemed guest, Dr. Abraham, to the podium.

DR. ABRAHAM Thank you, Kelley, and thank you, Josh, for the kind introduction. I thank *JADPRO* for inviting me I am really impressed by the audience, and we have almost 70% nurse practitioners, and I really respect nurse practitioners and Annie who works with me. She is sitting here. She is in Cleveland Clinic in the best program, so I really admire and respect the nurse practitioners, because Annie actually saves my day every day. If Annie was not there, I do not think I would be able to do what I do every day. So, thank you.

I am going to put a few cases that we can talk about. The way I understand oncology or medicine is through my patients. Before I get into the patients, as Kelley said, the story of breast cancer and the study of *HER2* positive is really fascinating. I finished my fellowship in 2001. In 2000 when I was a fellow, one of my patients – actually we were doing bone marrow transplant for breast cancer in 2000 sadly. Some of you are familiar with that. We used to do transplant. One of my patients was getting ready to go through bone marrow transplant for breast cancer. She was on the cover page of *USA Today* that day. I was rounding and then her picture was on the cover page. She was actually on the waiting list to get trastuzumab as a compassionate use. Just think of it: In 2000, she was in that group of women who were really fighting to get trastuzumab for compassionate use. We came a long way. Young people like

Annie, many of the young people have no idea how far we came. We came a long way. As Kelley said, now *HER2* positive is one of the most aggressive diseases, but it's completely changed. At that time, we were talking about trastuzumab, now we have nine or 10 different drugs. It's really great news for our patients, but as Kelley was saying, we still lose our patients with this aggressive disease. It's important for us to keep doing studies and finding new treatment, making sure patients can tolerate the treatment, and they can stay on the treatment. All of you play a key role in all of these things, from managing patients, the trials, and managing side effects.

Let’s get back to this. If you are taking notes, think about this: the things we are going to talk about: neoadjuvant treatment, adjuvant, then post-neoadjuvant and metastatic. Those are the four categories we are going to talk. Neoadjuvant: Let’s look at this patient. She is 54. She presented with a 3-cm mass a few months after her last mammogram. I'm sure you hear this story all the time: I just had my mammogram, now I have this 3-cm mass. Then the patient will say, did the radiologist miss that? Probably not, because here the biology says a different story. She has grade 3 tumor, ER/PR negative, and *HER2* positive. That’s one of the most aggressive subtypes. It is a fast-growing tumor. So, the tumor can grow in 3 months or 4 months. In this patient, let’s just say you are seeing this patient in the clinic, what’s the best treatment option? Judging from your answers before, I know all of you know the answer. What do you think? A, B, C, or D? Anybody want to say? B, absolutely. Neoadjuvant chemo. The way we look at this: any stage II and above, *HER2* positive, should

be considered for neoadjuvant chemo. I will talk about two trials: TRYPHAENA and NeoSphere. Those are the two trials I will talk about that led to the approval of this particular regiment.

TRYPHAENA: This is a complicated slide. It is a phase 2 study, chemotherapy plus trastuzumab, or trastuzumab plus pertuzumab. Just think, adding pertuzumab to a chemotherapy regimen. Pay attention to C. This is what we do mostly in the clinic: TCHP. I am sure some centers probably do AC followed by THP, and that's okay. This is the trial, and if you look at all three arms, all three arms did fairly similar. You can see arm C, TCHP, that's the standard we use, it is almost 90% free or disease-free survival and others are similar. If you look at the cardiac toxicity, again similar, look at the third column. This is more than 10% from the baseline. Similar numbers. TCHP is about 9%, 11%, 16%, and 11%. This established the standard of care as TCHP as the neoadjuvant regimen.

There is one more study. This is NeoSphere. Here the similar question: adding pertuzumab in neoadjuvant setting for *HER2*-positive locally advanced breast cancer. Again, it had three arms. Here this is docetaxel and trastuzumab. When the patients received this treatment before the surgery, almost 30% complete pathological response. When they received docetaxel, trastuzumab, and pertuzumab, nearly 50% complete pathological response. Then, just by giving the antibodies, with no chemo, almost 16%. So, if you look at adding pertuzumab to the neoadjuvant setting, increased the complete pathological response. This is the theme. If you add chemotherapy, trastuzumab, and

pertuzumab, almost 50% of the time, the patient will have a complete response. The summary, the same: addition of pertuzumab to the regimen increased the pathological response.

Then the question is why do we do it? If the patient has a complete pathological response, it's a predictor of long-term survival. That's based upon multiple other studies. This clearly explains why we go for neoadjuvant chemo.

Going back to this patient, we will do neoadjuvant chemotherapy with docetaxel, carboplatin, trastuzumab, and pertuzumab. The standard is TCHP every 3 weeks for six cycles, followed by – then the question is followed by what? If you look at all these trials, they used trastuzumab for 1 year. I do not know how you guys do in your practice: do trastuzumab by itself or do trastuzumab and pertuzumab. What's the thought? It depends how aggressive the early stage is. You are doing both and that's fine. Then you drop the pertuzumab, right. Just look at this patient, age 54, 3-cm tumor, let's say she has two lymph nodes. That's a really high risk and it is absolutely fine doing both, but if you look at NeoSphere and TRYPHAENA, didn't include trastuzumab and pertuzumab in the adjuvant setting, they used only trastuzumab. That's one. In general, if somebody is really high risk and they have to receive neoadjuvant chemotherapy, I will tend to do both. I am with you. That's what we would do too. In some patients, if they have a lot of diarrhea, a lot of side effects, then I might back off. Any questions or thoughts so far about what I have said? Very good.

One of the questions I get is, when we do neoadjuvant chemo, what's the chance of complete response? If somebody has ER positive and *HER2* positive,

it's about 50%. That's what I tell the patient: 50% chance of complete pathological response. If you look at our patient, the patient we just discussed, she has almost 70%, 60% to 70% chance of complete pathological response. That's what I tell her. I tell her when you go for surgery, it's almost 60% to 70% the surgeon is not going to find a tumor. My nurse practitioners usually ask me that question saying: "The patient is asking, what should I say?" And, that's what I say. That's pretty amazing. Just look at that with chemotherapy. Then, now, some of the adjuvant trials and some of the radiation trials are asking the question: how do we deescalate other treatments like surgery or radiation? Can we deescalate that? Again, I'll be happy to take questions on that.

Okay. Now we are moving to the adjuvant setting. Let's look at another patient. She's 61, she had a screening mammogram and was found to have a 1.1-cm lesion, biopsy confirmed ER 80% positive and PR 20%. This is the picture you always see. When someone is *HER2* positive, you will see high ER expression and low PR expression. That's what you see. And then HER2. In general, we are doing immunohistochemistry. I don't know who is doing FISH. Are any of the practices doing FISH? You are doing upfront FISH for everybody. Okay. We used to FISH upfront for everybody, and about 3 years back in the clinic system, we stopped FISH. We do IHC and then if there is 2+, then we go for FISH. I know some practices, west coast mainly, do – okay. You are not from UCLA, right? You are from UCLA. Dennis Slamon really believes in FISH. Oh, you are his nurse practitioner. You can give the lecture. I can come out. I should put a picture of him. Dr. Slamon really believes in FISH. I know that.

So, she has a T1cN0 tumor. Here what do we do? Neoadjuvant chemo, send the patient for surgery, or T-DM1? B, absolutely B. I'm really glad you said this because there is a dogma, now with the T-DM1 trial out, people are saying everybody should get TCHP. Not exactly. Not everybody should because TCHP is a toxic regimen. It has its own side effects. I tell the surgeons—and sometimes the surgeons push—she has *HER2*-positive disease, she should get neoadjuvant. Not everybody has to get neoadjuvant. It's always about optimizing treatment. Not everybody needs the most aggressive form of treatment. Again, that's based upon the APT trial here: about 400 patients were seen, less than 3 cm, then they received weekly paclitaxel plus trastuzumab for 12 treatments, and then the trastuzumab was continued. Almost 99% 3 years disease-free survival. This is really good. Here the trastuzumab is playing the most important role. Trastuzumab is playing the most important role, and then chemotherapy is probably helping a little bit. So, it's really important to make sure that we don't expose the patients to unnecessary toxicity by giving more aggressive treatment when we can treat them with this regimen.

So this is Sara Tolaney's paper. This is an update, this is 2019, with a 7-year follow-up and actually, she just updated that last week in ESMO too, consistent results and almost 94% disease-free survival in 7 years. Recently, I was taking a phone call from a physician on the west coast and she had a 2-cm tumor, ER/PR strongly positive, grade 2, and the oncologist was planning to do TCHP. I said probably you should just do weekly paclitaxel and trastuzumab. It's

tough. We think TCHP is the most appropriate regimen, or aggressive regimen, but we can always tailor the treatment based upon the biology.

This is Dr. Slamon's study BCRG006. This is one of the pivotal studies. NSABP trial, NCCTG trial, and this one, BCRG006. These are the three trials which really changed the way we treat *HER2*-positive breast cancer. Early-stage breast cancer, most of them are lymph node positive, but about 30% are lymph node negative. So, AC followed by paclitaxel versus AC followed by paclitaxel/trastuzumab and TCH (that's docetaxel, carboplatin, and trastuzumab). So, three-arm study. If you look at here: trastuzumab-containing regimen did better than AC following by T versus TCH. Trastuzumab-containing regimen such as AC followed by TH and TCH did better than non–trastuzumab-containing regimens, substantially better. In this trial, adding anthracycline did not make any major difference. In general, I prefer TCH as an adjuvant treatment in an adjuvant setting. I always prefer TCH, mainly because of the side effects listed here. You are potentially worried about leukemia, cardiotoxicity, when you are using an anthracycline-containing regimen. If I have a family member, I really want to make sure I am not exposing that person to toxicities. It's tough for us to manage. In general, I don't do this; I do TCH.

We talked about two trials in adjuvant setting. We talked about the APT trial: the weekly paclitaxel and trastuzumab. The second one is TCH. Now the question is: Is there any role for adding pertuzumab in the adjuvant setting? It's a trial which looked at pertuzumab. Here: AC followed by THP, or TCHP was the experimental arm. The other arm was without pertuzumab. This trial asked the

question: What's the role of pertuzumab in the adjuvant setting? Here you can see almost 5,000 patients were randomized. It's a huge trial. Predominantly, not positive patients. And pertuzumab, again the standard dose, 840 mg loading dose followed by 420 mg every 3 weeks. This was probably one of the most disappointing adjuvant trials which came out in the last 5 years. I was actually part of this trial. If you look at this one, there is no difference. There is absolutely no difference. Almost 5,000 patients were randomized, and then pertuzumab added probably $100,000 dollars more to this regimen. If you look at the subset of patients who actually benefited, it was probably the high-risk patients. That's not positive or ER/PR-negative patients. So, if you ask to whom do I give pertuzumab in the adjuvant setting? Really, the high-risk patients. Side effects were really okay. Diarrhea was the only thing really standing out at 4% versus 10%. Otherwise, patients did okay. Even the cardiac events were similar.

If you look at this patient. She is 45. She has almost a 4-cm tumor, ER/PR negative. Somehow, she was missed, otherwise, she would have gotten neoadjuvant chemo. *HER2* positive, four nodes positive. What will you do here? I just said that TCHP is not that – it made a difference. What will you do here? Here, I will do TCHP. I am fine in doing TCHP for this patient. She is really high risk. She has a 4-cm tumor, ER/PR negative, she has four lymph nodes positive, so she is really high risk. So, in high-risk patients, I am absolutely fine in doing TCHP. She will get TCHP.

Let's say somebody has a 2-cm tumor, ER/PR positive, node negative, we should not be giving pertuzumab in that setting. Any questions? Thoughts? The

role of pertuzumab is one of the most confusing for the clinicians. Let's talk about extended adjuvant treatment. We talked about neoadjuvant: we said TCHP is the standard. Then we talked about adjuvant: weekly paclitaxel/trastuzumab is an appropriate regimen. TCH is an appropriate regimen. In really high-risk patients, we can use TCHP. Those are the three regimens in the adjuvant setting.

Extended adjuvant. Let's look at a different patient. She is 45, again 4-cm tumor, ER strongly positive (90% or so), *HER2* positive and she has two nodes. She had TCHP. This is before the KATHERINE data came out, or somehow, she missed the neoadjuvant TCHP. She finished 1 year of treatment with trastuzumab and pertuzumab. Here, what should we do? C. Let's look at a few things here. ER positive. I will talk about that in a second. Most of the benefit was in ER positive. This is a patient I would put on neratinib. ER-positive patients are benefited the most. Then the question is: Do we know the role of neratinib in patients who are treated with pertuzumab? We do not know. But this is the subset of patients I would treat. This is the trial. Here if you look at *HER2*-positive patients, those who received 1 year of trastuzumab. In this ExteNET trial, patients completed the *HER2*-containing regimen, but in that trastuzumab was the *HER2* regimen, not pertuzumab. The patients were randomized between neratinib versus placebo. The primary endpoint was invasive disease-free survival and overall survival. If you look at the – hormone receptor–positive patients had actually the maximum benefit. One of the questions I get is: What's the benefit? And it's about 30% improvement in disease free survival. Hormone receptor–negative patients did not have much. If you look at the NCCN, the way

we put it in the NCCN, is hormone receptor–positive patients recommend considering neratinib. The side effects, again, it looks like many of you know neratinib very well, side effects are GI side effects. Kelley is going to talk about that in detail. It is very predictable. It's diarrhea, it's nausea, it's very predictable.

Let’s move on to post-neoadjuvant. Let’s look at another patient. She is 45, a T3 tumor, more than 5 cm, lymph nodes are positive, M0, ER/PR positive, *HER2* positive. She is a very appropriate patient for neoadjuvant. TCHP, that’s the regimen, and then she had bilateral mastectomy. I know a lot of people offer bilateral mastectomy. The pathology showed 1.9-cm tumor. What I said before: ER-positive patients receive complete pathological response only like 50% of the time. When an ER-positive patient, after neoadjuvant chemo, when the go for surgery, I always prepare them. I will tell them there is a 50% chance when you come back after the surgery there is going to be tumor. I do not want them to be upset. But ER/PR-negative patients I will be a little more positive. I will say there is less than a 40% chance of having a tumor. So, she has 1.9-cm tumor left, and micro met in one node. What should we do now? C. Right. T-DM1. So, that one trial just changed the landscape overnight. It's pretty amazing. So, this is the trial: patients are treated with trastuzumab-containing regimen, then when they have residual disease, the patients were randomized between continuing trastuzumab versus T-DM1.

If you look at all these trials, and I really admire the patients, the thousands of patients who went on all these trials. Just think about this. Even the trastuzumab trial and pertuzumab trial. When we were selecting this trial at

Cleveland Clinic, I still remember the conversations the doctors were having. We were saying how can we put a patient on T-DM1 when we know that trastuzumab is working so well, how do we know that we are doing a harm for the patient? That was one of the questions. One of the questions was how do we know, if we radiate patients when they are on T-DM1, how are they going to do? So, even the doctors were skeptical. I really admire the thousands of patients who signed up for these trials. That's the reason we are standing here and talking now. They received the standard dose, 3.6 mg/kg, for 14 doses or so. This is pretty remarkable. Almost a 50% reduction in invasive disease-free survival. Pretty remarkable results. As you all know, this is precedent in San Antonio and published in the *New England Journal of Medicine*. We knew the data would be decent, but we didn't expect it would be this remarkable when we were reviewing the data the day before the San Antonio presentation. It is really impressive. If you look at – I know it's fine print and you can't see much of this, but if you look, all subsets of patients benefitted by adding T-DM1. That's the key: all subsets of patients benefited. It didn't matter what age, it doesn't matter the ER/PR, or the grade of the tumor, or the node status. All subsets of patients benefited by adding T-DM1.

This is important. This is something you will be dealing with in the clinic. The blue is the T-DM1. Recently, one of my friends, she's 40-something, she had neoadjuvant chemo, she is going through T-DM1 and she is having a lot of fatigue. She called me and asked, is it common? You can see that fatigue is almost 50%. Grade 3 is fairly small, but fatigue can happen, and then nausea

about 40%, and then neuropathy. You can have neuropathy. There is a side effect to this regimen, so there is a price to pay for this regimen, but I think it is widely accepted because of the remarkable survival advantage. There are side effects. LFT abnormalities; I think we need to watch the LFTs. So, fatigue, neuropathy, and LFT abnormalities are something we need to watch.

Metastatic breast cancer – all of you are still with me? You feeling sleepy? We kind of finished the early breast cancer now, the neoadjuvant, adjuvant, extended adjuvant, and then post-neoadjuvant. Somebody has a question, yes?

AUDIENCE MEMBER: were patients on the hormone receptor blockage?

DR. ABRAHAM ExteNET study was neratinib versus placebo. They finished 1 year of trastuzumab, then they received neratinib, and they had endocrine treatment. They took endocrine treatment along with the neratinib. Right. Good question. Anything else? Any other questions or thoughts?

Let's move on to metastatic. Young patient, she's 39, a T2N1, more than 2 cm, lymph node positive, ER/PR negative and *HER2* positive. She had TCH in the adjuvant setting about 4 years back or so, and now she has multiple liver lesions. As you know, when the patient has metastatic disease, we always ask for repeating the biopsy and about 14% of the time it can change. About 8 years back or 10 years back, when we did biopsy, when we asked the pathologist to repeat the *HER2* or ER/PR, the pathologist used to get upset. Now we insist. We say, well, 14% of the time it can change the treatment. It can be a huge difference. Here I put it as ER/PR positive and *HER2* positive. What do we do

here? B. Taxane, trastuzumab, and pertuzumab. I put taxane, but we can talk about that. The first-line treatment of *HER2*-positive metastatic breast cancer has really changed in the past 5 or 6 years or so. Trastuzumab, pertuzumab, and docetaxel is the gold standard. Let me say it this way pertuzumab, trastuzumab, and a taxane. I use the term taxane because you can use docetaxel, that's the gold standard, but you can also weekly paclitaxel too. You can use T-DM1; let's just say if the patient progressed right after she received pertuzumab, then you can use T-DM1.

The trial which established the role of docetaxel, trastuzumab, and pertuzumab, in a metastatic setting is the CLEOPATRA trial. It's a phase 3 trial, TH versus THP. That's the trial which established the role of pertuzumab in this setting. This was really a remarkable trial. If you look at the progression-free survival, a substantial improvement when the patients received pertuzumab. And overall survival, almost 5 years overall survival. Again, I say this is remarkable, for a 35-year-old, it does not mean anything, but still this is pretty remarkable. Before the introduction of *HER2*-targeted agents, trastuzumab, the progression-free survival was probably 12 months or so. So, this is really remarkable, almost 5 years of overall survival. The side effects: this is a fairly well-tolerated treatment. Neutropenia is seen, but the pertuzumab did not really change the neutropenic rate, and febrile neutropenia is slightly increased. Here we used pegfilgrastim. So, in THP regimen, in general we use pegfilgrastim. Leukopenia is seen and diarrhea. Here we are not seeing much difference, about 5% versus

8% or so, but TCHP in the adjuvant setting it is much more when we combine that with carboplatin.

CLEOPATRA conclusions: Additional pertuzumab clearly improved the progression-free survival and overall survival. This is the standard of care. Here we put the duration of pertuzumab. How many cycles usually in your practice do you give pertuzumab? If you look at the CLEOPATRA trial, that's THP, that's docetaxel, trastuzumab, and pertuzumab every 3 weeks for six cycles. That's the way the trial was done. That doesn't mean I am going to stop the chemotherapy for every patient at six cycles. I tell them the trial used six cycles, but we can potentially continue beyond six cycles. There is no hard-and-fast rule saying we should just stop at six cycles. That depends upon how much the patient is responding and what side effects the patient is having.

Next patient. This is a 39-year-old young patient, T2N1, ER/PR negative, *HER2* positive. She had TCH adjuvant setting, biopsy proven multiple liver lesions which are ER/PR positive and *HER2* positive. She was treated with THP, docetaxel, trastuzumab, and pertuzumab for 2 years. She did well. Now she has lung lesions, multiple lung lesions. How do we treat? This is second line. First line is established, that's THP. Second line? C. Second line, it's T-DM1. Again, we can use other agents, other combinations, but this is the standard, the preferred standard. That's based upon this trial, the EMILIA trial. T-DM1 versus capecitabine plus lapatinib. This randomized trial in patients who had trastuzumab in metastatic setting. You can see trastuzumab, not pertuzumab. When this EMILIA trial was designed, pertuzumab was not established as the

standard, and then many of the patients in this trial actually came from around the world. So, T-DM1 versus capecitabine and lapatinib, which was the standard at that time. An improvement in progression-free survival for T-DM1 compared to capecitabine and lapatinib. This established in a second-line setting, T-DM1 is the standard.

This one of the trials we did. Kim is sitting here; she was my research nurse. We did this trial. Can we improve upon T-DM1? That was the question we asked. As I said, T-DM1 is the second-line standard. Can we add neratinib to T-DM1 and increase the efficacy of T-DM1? It is a phase 1 study. We started at 120 and escalated the dose up to 240. All these patients had prior trastuzumab and pertuzumab because it is a recent study. We had almost 63% response rate. We were really impressed by the response rate in this setting, almost 63%. Of course, patients have diarrhea, because the patients are getting neratinib. Kim did a major role in educating all of our patients. We actually had a protocol. We used to call the patients the day after they go home and make sure they take their prophylactic medicines. Diarrhea was the most common side effect. In this study what we found was the recommended dose for neratinib, in combination with T-DM1 is 160 mg. In the extended adjuvant setting, the dose is 240 mg. In here we went up to 240, but the patients had so many side effects, we had to back off to 160. We finished the phase 1, and then actually we did a phase 2, and we actually completed the phase 2 also. This was published recently in this year. There were a few other things which were interesting. We looked at the

HER2 amplification in the blood and if they had high *HER2* amplification, they responded substantially. That's something we will follow up.

First line we established: that's THP. The second line we established: T-DM1. T-DM1 plus neratinib is not a standard yet. We just completed our phase 2 study and we will do a phase 3 after this and if that comes back as positive, then potentially we can change the standard of care.

Let's look at the third line. Young patient who had THP (first line), and in second line the patient received T-DM1. Now the patient has progressive disease. Again, after second line, it's kind of an art. There is no standard of care. First line we can say there is a gold standard with pertuzumab, second line is T-DM1, after that, it is kind of an art. What do we do here? There is no perfect answer here. If she is ER/PR positive, there is an option, potentially we can combine with palbociclib too. Here the answer I am looking for is D. The patient has not seen lapatinib, so lapatinib with capecitabine, or potentially neratinib with capecitabine. Those are the potential options. Third-line setting, multiple regimens we can use. Even we can use trastuzumab and lapatinib if we do not have to use chemotherapy.

This is the phase 3 trial which actually established the role of lapatinib in metastatic setting. Lapatinib plus capecitabine versus capecitabine by itself. So, lapatinib is an option. This is presented at ASCO, recently the NALA trial, which asked the question: Can we do capecitabine and neratinib versus lapatinib and capecitabine? Here the neratinib dose is 240 mg, capecitabine is 1500. Here you can see the capecitabine is 2000. So, lower dose of capecitabine, but the full

dose of neratinib. The patients had prophylactic diarrhea medicine. When this study was ongoing, and we were part of the study, I was kind of skeptical because this is a pretty tough regimen, capecitabine and neratinib. But it met the primary endpoint which is progression-free survival and significant improvement in progression-free survival when neratinib plus capecitabine was compared with lapatinib and capecitabine. I know we will talk about the side effects of this regimen. The diarrhea side effect was comparable actually and the two regimens were not that different. If you look at all grades, it's 83%, but here grade 3, it's 24% and then 13%. Even the lapatinib and capecitabine had diarrhea, so 13% versus 24%. That was the one which really stood out, but the hand-foot syndrome was higher in the lapatinib and capecitabine. That's probably because the capecitabine dose in this arm was higher than the capecitabine dose here.

In conclusion: NALA met its primary endpoint, which was progression-free survival, when potentially combining neratinib plus capecitabine is superior than lapatinib and capecitabine. The FDA hasn't approved this regimen yet, but it is being reviewed.

Now, moving on to some of the newer treatments. Let me pause. Ask me questions. Metastatic first line THP, second line T-DM1, third line is lapatinib and capecitabine or we can potentially; if the NALA trial gets FDA approval, then it's neratinib and capecitabine.

Moving on to some of the newer agents, tucatinib, which is a novel small molecule, which is a tyrosine kinase inhibitor. It is a TKI. It is a pretty powerful TKI. There are multiple trials which looked at tucatinib, phase 1, phase 2, and

phase 3, and there is a trial which looked at tucatinib plus T-DM1 similar to the NSABP B-10 we just showed. This is actually really interesting. If you look at patients who are heavily treated with multiple regimens, the tucatinib plus capecitabine had a really nice response, almost 83% response rate. This is tucatinib and trastuzumab. This is tucatinib with capecitabine and trastuzumab, 61%. This is a really good response rate. Most of them are partial response. So tucatinib is a really promising drug. This is phase 1b trial; it's combined tucatinib with T-DM1. It is similar to the neratinib trial. The progression-free survival was about 8.2% and clinical benefit rate was about 58%. We reported about 63% with neratinib, so it's similar. Tucatinib again, they are actually waiting for a major study to come out hopefully, at San Antonio, it's known as HER2CLIMB. It's similar to the NALA trial; it's a randomized trial. We'll see. If that's positive, then potentially tucatinib will come to the clinic.

This is DS-8201, another antibody-drug conjugate. We talked about T-DM1, which is an antibody-drug conjugate. This is another antibody-drug conjugate. Like any antibody-drug conjugate, it has a humanized anti-*HER2* antibody. It has a chemotherapy arm and a linker molecule. This is a really promising drug too. There are multiple trials going on with this drug. Again, heavily pretreated patients, seven prior lines, almost 60% overall response rate. So, it's a really promising drug. One of the side effects: pneumonitis. There is a real concern for pneumonitis. How many of you are participating in the DS-8201 trial? We are opening two trials with this drug. One in *HER2*-low patients, meaning 1+ or 2+, so it is active in even 1+ or 2+. And then we are opening a

trial in patients who progressed on T-DM1, so in third-line setting. There is a trial in second-line setting too. There are multiple.

Lastly, I will talk about CNS. Again, this is a major problem. Unfortunately, it is a major problem. A large number of our patients develop brain mets. Almost 30%, 30% to 55% of patients. This is a huge problem. These are some of the predictors: young age, *HER2* positive, high-grade tumor, large tumor, and I am sure many of you have these kinds of patients. I had two young patients; both were like in their 30s. One patient did amazingly well, and the second patient progressed in less than a year with rapid progression in the brain. They were diagnosed around the same time and they got connected. Of course, the patient who was doing really well is still doing really well, and there is a huge guilt and it's really a tough situation. So, we don't know who is going to develop brain mets and who is going to have rapid progression of the disease. There are multiple potential agents: neratinib is one of the agents, tucatinib is one of the agents, veliparib, immunotherapy, and there are multiple potential options. This is a trial we just looked at with neratinib plus capecitabine in brain met patients. This is actually really interesting. If you look at the capecitabine dose of 750, neratinib is 240. They had to have at least one CNS lesion. Almost 50% partial response in this study. That is again, as you know, brain mets is one of the toughest diseases to crack. Again, we don't know why the increased met; it could be biology. Because trastuzumab and pertuzumab, or even T-DM1 have bigger molecules that do not penetrate the brain, some of the smaller agents like neratinib penetrates the brain higher. In conclusion, almost a 50% overall response rate

when neratinib plus capecitabine was used in *HER2*-positive patients. NCCN has included this as a potential option in patients who have brain mets.

They looked in NALA, in subsets, actually the patients who received neratinib and capecitabine actually had lesser CNS events. Here this is a complex problem, but it is increasingly common. Other patients are doing really well with systemic treatment, and then they progress in brain. I have a young lady who is going through her third or fourth Gamma Knife – Gamma Knife and whole-brain radiation multiple times. NALA and the previous trial gives us an option potentially we can use neratinib and capecitabine in this setting. I'm done. Thank you for staying awake.

MS. MAYDEN Thank you so much. That was an awesome job. Can you see why I say he is the human encyclopedia of breast cancer? I'm merely a footnote in the index, but hey. So, we are going to switch gears a little bit here and talk a little bit about trastuzumab biosimilars because they really are an idea whose time has come. It's an idea that has been out there since 2010 when we had the Biologics Price Competition and Innovation Act, which outlined and abbreviated Pathway for Biosimilars 2009, and then it was signed by President Obama in 2010. It has taken that long for biosimilar uptake in the oncology space, but many of you are already experiencing this at your institutions and on your formularies, and we are going to continue to experience that. When we think about *HER2*/neu-positive breast cancer and biosimilar trastuzumab, this is going to be part of what we are doing for our patients.

Case study says a 54-year-old female with *HER2*/neu-positive metastatic breast cancer is to receive chemotherapy and trastuzumab biosimilar. She voices concerns about receiving the biosimilar. Which of the following is your most appropriate course of action? Tell her it is okay since biosimilar trastuzumab is a generic of reference trastuzumab? Tell her you understand and withhold therapy? Explain the rigorous testing process for biosimilars and address any other concerns? Switch her to therapy with neratinib and capecitabine? Any guesses? Right: Explain the rigorous testing process for biosimilars.

When we think about a biosimilar, the biggest question clinicians have is: can we do this, is it safe, what does it mean? The answer is: yes, we can do that, and we are doing that. When you think about a biosimilar and how that comes to market, it's not like a generic medication. Biosimilars are not generics. Biosimilars are biologic large molecular weight proteins, which are heavy weights. They are made in living systems and because of this, they are subject to inherent variability. We cannot take them like small molecule drugs and make them to exactness in a laboratory setting. Because of that inherent variability, we can't say they are generics, but we can say they are highly similar. A biosimilar is highly similar to the reference product. Biosimilar trastuzumab is highly similar to trastuzumab. That's a process strictly outlined by the FDA. It's a stepwise approach to gaining a totality of the evidence. Based on the totality of the evidence and scientific justification, then manufacturers, if they can prove that this is truly highly similar, can be granted biosimilar status. To get that, they have to prove, by the FDA definition, that there is clinically meaningful difference in

terms of the biosimilar and the reference product. This also means no difference in safety, purity, or potency of the product. This is proven with a phase 3 comparative study. We can say that biosimilars are safe and we can incorporate them. Why do we need them? Why did it come about in the first place? They came about in Europe in 2006 for the same reason, and that is because more and more patients are living longer. Our *HER2*/neu-positive women. We are doing a better job. Trastuzumab has done a great job. Women are on chronic therapy and this can go on for years. Had a patient just the other day, I discussed with someone, who had been on trastuzumab for 10 years. I don't know if you do that or not, but they just were afraid to take her off. As more and more of us age, and more and more patients need chronic therapy, there is an increased demand for these biologic products, so the cost of the parent drug is one thing, and if we didn't come up with a way to have more affordable options, and access to more product, then ultimately what happens is somebody ends up getting restricted access. Our payers start to get cranky about paying for the long-term therapy. The biosimilar movement came as a way to introduce these highly similar products at 15% to 30% cost reduction. We do know from the European data that their country has saved billions of dollars and more patients have been able to access the biologics. That's what we need. There was an unmet need and cost was a problem. The adverse event profiles of the biosimilar and the reference product are highly similar. If they were not, the drug would not achieve biosimilar status. That comes to speak to safety. This patient that has concerns about receiving the biosimilar, the appropriate thing to do would be to sit down with her

and explain the FDA has – I don't go into in vitro, in vivo, PK studies and the clinical comparative study, I just say the FDA has a very strict process, as strict as trastuzumab when it got approved. It makes the patient feel comfortable about getting the product.

These currently are the FDA-approved biosimilars in the US. You can see that only one currently is commercially available, and that's trastuzumab-anns. Some issues with biosimilars by and large, absolutely the first issue and the largest issue is that advanced practice providers and patients are misinformed. There is a lot of misinformation. People don't understand the process. Formularies have just dictated to people "you will do this." There has been a lot of stuff happen in all of that transition. Some stuff should happen, and some stuff that shouldn't happen. How do we best educate the patients? Do we need to reconsent? A lot of these issues you need to discuss, but the main thing we, as advanced practice providers, have to really do is understand the process. If you don't understand the process, and you are not comfortable with this, I encourage you to go to the FDA. The legislation is there. Their website has the legislation, the act, and it outlines the process. There are even CME modules you can do to help get yourself educated, because if you are not educated, you cannot educate your patients, and trust me, there is a lot of stuff out there in the public that is trying to educate the patient that shouldn't be.

Another issue is benefits. People say, well, that doesn't really seem like an issue. So, we have increased drug access and lower cost. This can sometimes cause patent wars, companies filing suits to hold onto their drug patents because

as more and more cost reduction comes and we increase access, then parent companies can sometimes not be as profitable.

Choosing between the parent drug, substitution. You just saw in this previous slide we have multiple biosimilars right? Only one available right now, but they all will come and be available. So, what do we do? How do we pick which biosimilar? What if they are all on our hospital formulary? The problem becomes with substitution. What do you do if the patient is on trastuzumab, the patient gets switched to trastuzumab-anns, the patient gets switched to another biosimilar, and the patient gets switched back to brand name trastuzumab? There is no data for that, but it's possible that could happen in the systems. That's substitution. It's important for us to understand the difference between substitution and interchangeability. They are not the same concept. Interchangeability is a concept that has to do with – the drug could be substituted at the level of pharmacy and may or may not have to notify the provider depending on the state laws. So, when you are thinking about going back and forth among the molecules, the better language to use is switching or cross-switching, switching or switch back, not interchangeability. That might become an issue and what do we do? There is no data about switching among all of these products, but if third-party payers decide this month they want this one, and next month they want that one, what are we going to do. That's a potential issue.

Extrapolation of indications to other settings. We know that manufacturers, when they go for biosimilar status only have to prove biosimilarity in one indication for which the reference product is indicated. If they have good data and

scientific justification is strong, then they will be able to get extrapolation where they will have ability to use their drug in all indications for which the reference product is indicated. However, what happens if, in some cases, they don't have the data to get extrapolation in all indications, but people get the process confused and don't know to go look and make sure. That could be a potential issue.

Possible PK/PD differences. I don't really see that as a huge issue because there is a human PK/PD study demonstrating biosimilarity and that data has to be pretty strong, so any problems with PK/PD, I think pretty much the degree of uncertainty is disappearing toward the top of the process. Safety, immunogenicity, and long-term follow-up. There are some people who argue that as you get toward the biosimilar developmental pathway and you have completed the PK study, you don't really need to do that phase 3 clinical comparability study to prove safety and immunogenicity are not different. That's not true. You do need that phase 3 comparative clinical study. That's where you are going to see those immunogenicity signals, the potential for the immune system to be turned on by this molecule versus the reference product. Remember, biosimilarity says no difference in safety, purity, and potency of the product. I don't see that as much of an issue, but in the post-marketing phase, phase 4, if you see an adverse event, we do have that responsibility to report that. A lot of things happen in the phase 4 clinical trials or the pharmacovigilance phase.

You just saw in this previous slide – look at the dates these were approved by the FDA, and we still only have one on market. There is a time lag between FDA approval and availability. Some of that does have to do with patents going off or companies file lawsuits; they file new lawsuits trying to keep the patent.

Clinical pearls for trastuzumab biosimilars are we have a significant need. We need them. They will increase patient access and affordability. That was the whole point in the legislation. Trastuzumab biosimilars are marketed abroad. They are here with us now. Efficacy and safety are comparable to the reference product. As practitioners, we are going to have more and more demand to know about these products because we are going to be the ones educating patients, talking to patients, and managing patients. You already do this. You are managing patients on chronic therapy, right? So, it's important for us to know.

We are going to talk lastly a little bit about just a couple of common adverse events with *HER2*/neu-positive therapies. First of all, case study, 49-year-old female, infiltrating ductal carcinoma, ER/PR negative, *HER2*/neu positive. She is continuing trastuzumab after TCHP neoadjuvant. Start of chemotherapy her left ventricular ejection fraction is 65% with a global longitudinal strain of 25.5%. At 3 months follow-up, her left ventricular ejection fraction is 58% and the global longitudinal strain is now 19. This represents a 25% reduction in the strain from baseline. She has no symptoms. What do you do? Continue trastuzumab until 16% drop in left ventricular ejection fraction? Hold therapy and repeat testing in 6 weeks? Continue therapy and consider

cardioprotective measures? Change to trastuzumab biosimilar? Collaborate with cardio-oncology? What do you think? Okay, we will talk about that.

Common toxicities with *HER2*/neu-targeted therapies are all listed here, but at the bottom of the slide is cardiotoxicity. This is one of the most important long-term side effects that we need to focus on. It can occur in monotherapy or combination therapy. Why do we need to focus on it? Again, our people are living longer, but if we cure your breast cancer or we have you to have stable disease for long term, but you have cardiomyopathy or congestive heart failure, what happens to your quality of life? What happens to your will and abilities? When we think about treatment-associated cardiotoxicity, it is a hot topic. We know that cardio-oncology is emerging, and I am really happy to know that there are a lot of advanced practice providers who are actually doing this role of being a cardio-oncology advanced practice provider. I think that's amazing. Again, our people are living longer. People greater than age 65, and that's a lot of our breast cancer patients, are the people who are most likely to die from cardiotoxicity or have these long-term decreased quality of life. As survivors increase, we will continue to see this number of patients, so we have to get strategies up front to mitigate cardiac toxicities. This is another thing we have to plan up front. Anthracyclines, *HER2* antagonists, and radiation in the heart field all are risk factors for cardiotoxicity and you all know, you have taken care of patients who have all three of those in combination.

When you look at what happens with cardiotoxicity, the most common thing is an asymptomatic left ventricular ejection fraction decline. We know that

patients have secondary cardiac events, and 7% of patients who have had trastuzumab have had this, and 19% of patients who have trastuzumab and chemotherapy, predominantly anthracycline-based chemotherapy, are at risk for this. It is important to think about cardiotoxicity. It is a progressive process. It begins with an asymptomatic state with this decline in left ventricular ejection fraction and then progresses to cardiomyopathy and congestive heart failure, so the earlier we pick up on this and the earlier we intervene, the more likely we are to stop that process. We should avoid concomitant use of trastuzumab and anthracyclines. This is usually reversible if we manage correctly. For example, with our trastuzumab and biosimilar trastuzumab would be exactly the same. You get your ejection fraction and protocol says if you have a decline by greater than 16%, you hold for 4 weeks and then you repeat, and if you have returned to baseline, you can reinstitute therapy. You can wait another 4 weeks if you need to and reinstitute, but if you are not monitoring, then you are not going to know. I know you all just said, well, of course we are monitoring, why is that a point? But if you go look at the data, it's a problem.

Risk factors for cardiotoxicity vary between anthracyclines and trastuzumab. They have many things in common. For example, older age, people who have had concomitant therapies, combined therapies, cumulative dose. We know for patients who get greater than 250 mg/m^2 of doxorubicin had increased risk. If it's epirubicin, like the European setting, it's 600 mg/m^2, and in both groups, note that it's anybody who has a preexisting cardiac condition. I just ask you to think about in your everyday practice what you have been doing with that

really. Here's patient history, you've got the plan, you're going to manage them. You are assessing symptoms. Echo was good. Ejection fraction was 58%. You are good to go. Patient is doing well. But are you thinking beyond that point? Because we are now called to think beyond that point when we are looking at managing cardiotoxicity, and I will tell you what we are being called to do.

Preexisting conditions that are there. What are those risk factors that we have to be aware of? Smoking, hypertension, dyslipidemia, obesity, and diabetes. Those are five risk factors we all need to get into our head, because patients on these therapies, if they have two of those present, are now considered high risk for cardiotoxicity, and our management is going to be different because of that. What do we do? We always do our upfront assessment. I don't think anybody is falling down on that. We get a plan. We consider do we need to get some strategies in place for prevention. I want to mention that global systolic longitudinal strain is emerging as a gold standard for predicting left ventricular dysfunction. I would like to see a show of hands, how many in this room, when you are looking at that ejection fraction are also making a note in your document about what that readout is. Great, so, we definitely have a lot of people who are doing that. If not, start doing that. You will find that on your echocardiogram report, it's there. Speckled tracing from the echo gives us this number, and what it is is a measure of the longitude of the myocardium, and the strain number is the myocardium when it goes from resting to systolic. That number, if you have greater than a 15% change from the baseline global longitudinal strain, that is much more predictive of cardiac dysfunction earlier

than waiting on your ejection fraction. Now, it's important to be clear that in treatment and changing our treatment and holding therapy and reinstituting therapy, we currently do not go by this number. That's the subject of clinical trials, but it's important for us to know because if we pickup on this, but our ejection fraction is still great, we would collaborate with cardio-oncology. This is at a point where I would say I've observed this, let's go ahead and get a cardio-oncology consult. We can look at the optimal type of therapies. You heard Dr. Abraham say drug de-escalation, therapy de-escalation. We saw the APT trial data where patients with smaller tumors could get around having anthracycline-based therapies, so minimizing that. We can hold, dose reduce as needed. And treatment with ACE inhibitors and beta-blockers, and ARBs as well, these are standard of care for people who have heart failure. People with heart failure or cardiomyopathy, they are on these medications. That's in the label. What is off label is the use of these medications to prevent cardiotoxicity. Starting people on these medications at the beginning of therapy. There are multiple clinical trials that are looking at that. I do not want to say any particular drugs because there are several drugs out there that we may see in the future that will become a new standard of care, an emerging therapy, when we think about those trials. There are also some trials that are looking at statins to give people up front as a cardio-protective measure. If our patients are high risk or they are getting bigger doses, we know that we can also give dexrazoxane. It does have efficacy as a cardio protectant, but it does not compromise outcome. Lastly, think about liposomal doxorubicin. It's also an option in some cases.

One point I want to make is this: this statement says, “post-treatment echo in asymptomatic patients at increased for cardiac dysfunction.” When you look at the data across the country and you audit charts, post-therapy, women are fine, they are young, they are healthy, they are done. Four cycles AC, and they’ve done their year of trastuzumab, intact, no symptoms, cardiac function. However, if they have two of those risk factors, overweight, smoking, maybe they have hypertension, and they had those treatments, they should be marked in your chart as high risk patients. If they are marked as high-risk patients, it is standard of care to obtain an echocardiogram at 6 months to 12 months after the completion of therapy. If you haven’t been doing that routinely, that is now the standard of care.

These are some emerging cardiac biomarkers. We are not ordering these routinely in the clinic setting. They are the subject of research. Brain natriuretic peptide, troponin I, and N-terminal proBNP. How they are using these, and troponin I is really the one that looks the most promising. They check these markers before they give therapy and they check them at strategic times after therapy, certain hours, 72 hours, 96 hours after therapy, and what they are finding is, if you see an elevation in troponin I after administration of therapy, that is a predictor of cardiac dysfunction. More to come on those.

Importantly for us as advanced practice providers, the things that are here, we do this all the time, but we are now being called to do this in collaboration with all of our other specialties. For a long time, it has been easy to say your blood pressure is up, we need to get you over to your primary; your blood sugar is 400

today, we need to get you over to your endocrinologist. That isn't acceptable anymore; we have to manage these things as well. We have to comanage. All of these things listed here, we do, but we need to take a more active role in these patients at risk. Probably the most challenging of all of these is smoking cessation. It's the subject of multiple talks and we all feel somewhat defeated, I think, in our efforts with that. No fault of our own, it's just addiction is so ingrained. We are not alone in guidance. We do have a clinical practice guideline now from ASCO on how to manage our patients at risk for cardiac dysfunction. There is also guidance in the NCCN guidelines under survivorship, but it is not as detailed as this. This is a new guideline that came out in 2017 to help us in our efforts to do this.

The last thing I am going to move on to—I am going to skip that case study—is diarrhea, because we heard a lot about diarrhea this evening, particularly associated with neratinib. The biggest thing it can do, aside from what's listed here, is it can make our patient come off therapy. If our patient comes off therapy, then we have a compromise in efficacy. What the good news is, is advanced practice providers can manage diarrhea. It's a common thing. We heard about that today. In the ExteNET trial, 40% grade 3 diarrhea. That's where we start getting worried. What happened is, in that ExteNET study, somebody asked the question in the back, were patients on the hormone receptor blockage? Yes, they were, but in the ExteNET study patients were not on mandatory diarrhea prophylaxis, so there was a high grade of this diarrhea. People got wise and said we need to give some prophylaxis up front and see if

we can get our patients to stay on therapy, and better manage them. That was the birth of the CONTROL trial, phase 2 sequential cohort study, looking at upfront mandatory prophylaxis. You can see all of the arms here, starting with loperamide, loperamide plus budesonide, loperamide plus colestipol, and that was structured and as needed. Importantly, at the bottom of the slide is dose escalation, so starting the patient at three, four, six tablets, or four, five, six tablets. Remember the neratinib dose is six 40 mg tablets, 240 mg a day. With that dose escalation, you can use as needed loperamide. There is not a slide about this, but I can tell you what the data says and that is any of those cohorts you use are better than doing nothing at all. Any of those are going to keep the patient on therapy longer. Dose escalation, very promising, so is the budesonide and colestipol arms. Budesonide is actually in the package insert, but any of these are better. What we have found is when you institute upfront prophylaxis with neratinib – again, this is advanced practice, is now educating on a couple of things. Here is your neratinib. Here is what we do for your diarrhea. Here is my number. Here is your written plan, and you call me. Because it is not if you will get diarrhea, it is you will get it. Making sure that the patients have it. It's diarrhea for a month. It occurs early and then it dissipates. Making sure that you have patients up front, we have common sense about BRAT diet, hydration, you guys do that every day, see patients, check electrolytes, put them on some IV fluids, but if we will manage this neratinib diarrhea, patients can stay on therapy for a year. In the NALA trial, they had already learned too, because they had mandatory prophylaxis.

Summing it up, the role of advanced practitioners in managing patients on *HER2*/neu therapy. We have to have knowledge of the treatment and patient selection. Get our baseline characteristics particularly in terms of their cardiac function. Do a GI history and a GI assessment; and GI assessment every time we see the patient. Monitor for toxicities and patient adherence to oral medications. If they are coming in and you have told them everything, and you've done your job, and you're doing dose escalation, and they have diarrhea, you have to think maybe they are not doing what I told them with antidiarrheal. Proactive self-management for toxicity and report any untold side effects.

In conclusion from our presentation – we know the historical standards for care for *HER2*/neu-positive are being impacted by the emerging data. Data supports the use of pertuzumab as combination therapy in the neoadjuvant, adjuvant, and metastatic settings. Pathologic complete response is now predictive of outcome and also directs therapy in the adjuvant setting point to a new standard of care. Breast cancer patients fortunately are living longer, and therapy is being refined in the metastatic setting with specific guidelines for addressing CNS metastases.

JOSH EPWORTH Thank you all and thank both of our excellent speakers for this wonderful – and our wonderful audience tonight.

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